

Attorney Docket No.: A33432 (070050.1354)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Applicants : Modak et al.
Appln. No. : 09/746,670 Examiner : Bennett, Rachel M.
Filed : December 22, 2000 Group Art Unit : 1615
For : ANTI-MICROBIAL MEDICAL DEVICES CONTAINING
CHLORHEXIDINE FREE BASE AND SALT

OFFICIAL

**DECLARATION OF SHANTA M. MODAK
UNDER 37 C.F.R. § 1.132**

I hereby certify that this paper is being submitted to the
United States Patent and Trademark Office via facsimile to
Technology Center 1600 at 703-872-9306 on August 11, 2004.

Peter J. Shen

52,217

Attorney Name

PTO Registration No.

Signature

August 11, 2004

Date of Signature

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

I, SHANTA M. MODAK, hereby declare as follows:

1. I am a co-inventor of the invention disclosed and claimed in the present United States patent application.
2. I am an employee of Columbia University which is the assignee of the present United States patent application.

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3. Upon entry of the Reply Under 37 C.F.R. § 1.111 submitted herewith, Claims 1-8, 10, 12, 13 and 17-24 will be pending in the present patent application.

4. Each of the pending claims requires treatment of a catheter with a solution having at least a combination of chlorhexidine free base and water-soluble chlorhexidine salt in a weight/weight ratio of between about 1:1 to about 1:5.

5. I have reviewed the Office Action mailed by the U.S. Patent and Trademark Office on February 13, 2004 for the present application. I have also reviewed United States Patent No. 6,261,271 to Solomon et al. ("Solomon") and relevant portions of the Merck Index, which were cited by the Examiner in the February 13, 2004 Office Action.

6. Solomon relates to chlorhexidine-containing medical devices. Solomon's devices feature chlorhexidine bulk distributed throughout a polyurethane base layer which, in addition, may have a coating of chlorhexidine on the base layer. See Solomon, col. 5 at lines 47-52 ("The article of the invention having bulk distributed chlorhexidine may be steeped in a solvent solution of chlorhexidine ... An effective coating of chlorhexidine may be obtained when the steeping solution contains from about 1-25%, preferably about 5-15% of chlorhexidine."). Solomon does not, however, disclose or suggest treating catheters with a solution containing, at least, chlorhexidine free base and chlorhexidine salt as required by the presently claimed invention. We discovered that such

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treatment provides improved anti-microbial effectiveness through an increased uptake of chlorhexidine into the catheter. Unlike the presently claimed invention, Solomon also does not disclose or suggest catheters that are produced by such treatment.

7. The Merck Index discloses tetrahydrofuran as a solvent for use with polymers. The Merck index also indicates that tetrahydrofuran is miscible with water and alcohols. However, the Merck Index does not disclose or suggest using tetrahydrofuran in combination with an antimicrobial (such as chlorhexidine) to treat a medical device such as a catheter, as presently claimed. Further, nowhere does Solomon disclose combinations of chlorhexidine with tetrahydrofuran, or with any related compounds. I believe that the fortuitous combination of Merck with Solomon, though proffered by the Examiner, would not have been made by a person of ordinary skill in the art.

8. Solomon was cited by the Examiner as an independent basis for an obviousness rejection under 35 U.S.C. § 103(a). I provide this declaration to explain why, in view of Solomon, one of ordinary skill in the art would not have reasonably expected that treating a catheter with a mixture of chlorhexidine free base and chlorhexidine salt could successfully make a catheter exhibiting prolonged antimicrobial effectiveness. We discovered that such treatment surprisingly increased uptake of chlorhexidine into the catheter and consequently imparted to these catheters surprisingly effective and prolonged microbial resistance. See United States Patent Appln. No. 09/746,670, ¶ 0011.

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9. In fact, Solomon indicates that attempts to solve the very problem solved by the present invention - that is, adherence of an antibacterial agent to the plastic article - had been nothing but unsuccessful. See Solomon, col. 1 at lines 45-46 and col. 2 at lines 28-32 ("Many attempts to solve the problem of infection have been directed toward adherence of an antibacterial agent to the plastic article ... satisfactory solutions have not yet been disclosed, particularly for medical articles, such as catheters..."). Notably, Solomon does not use chlorhexidine free base and chlorhexidine salt alone as the antimicrobial, and nowhere proposes that use of a chlorhexidine coating - instead of the large amounts of chlorhexidine bulk distributed throughout the matrix of the catheter - would successfully prevent infection caused by introducing catheters into the human body.

10. Furthermore, Solomon would have discouraged a person of ordinary skill in the art, such as a physician, from using a catheter that has been treated with chlorhexidine free base and salt - ostensibly in order to successfully increase chlorhexidine uptake and prolong antimicrobial efficacy. Any such claim would likely have met with suspicion by a practitioner in the field. Indeed, Solomon fully admits that chlorhexidine on the surface layer of the medical article would be rapidly released. See Solomon et al., col. 3 at lines 19-20. Accordingly, Solomon clearly would have directed a person of ordinary skill in the art to avoid using a catheter that had been treated only on its surface with a solution containing a mixture of chlorhexidine free base and chlorhexidine salt; otherwise face malpractice! In light of Solomon at that time, a medical doctor could not - under any circumstances - have attempted to implant a catheter having only a surface-treatment of

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chlorhexidine free base and chlorhexidine salt. On this premise, Solomon instead resorts to bulk distribution of chlorhexidine throughout the matrix of a catheter as a solution to the problem of providing long-lasting antimicrobial efficacy. *See* Solomon et al., col. 3 at lines 21-22. In direct contrast, the present invention relates to a catheter which has been treated on its surface with a solution comprising both chlorhexidine free base and a chlorhexidine salt and unambiguously demonstrates that catheters treated only on its surface with such a mixture exhibit long-term antimicrobial activity. This finding was absolutely unexpected at the time of the invention, and would have been even more so in view of Solomon's observations that chlorhexidine was rapidly released from the surface of the catheter.

11. I also provide this declaration to explain why the Examiner's conclusion that the presence of tetrahydrofuran in the Merck Index, in view of the Solomon reference, renders the present invention obvious, is unfounded. There are many solvents listed in the Merck Index including many that were known to be both miscible with water and considered potentially useful as a solvents for certain large polymers. The mere disclosure of tetrahydrofuran, among hundreds of solvents in the Merck Index, would not have reasonably provided any specific suggestion or credible motivation to combine the two references as the Examiner has proposed. The Merck Index is little more than a listing of compounds and therefore cannot provide the explicit use of tetrahydrofuran with the medical articles or related methods described by Solomon.

12. The converse is also true. Nowhere does Solomon suggest to combine its chemical mixtures with tetrahydrofuran. A person of ordinary skill in the art

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would derive no such suggestion from Solomon either. Moreover, the solvents that are explicitly recited as suitable would have provided no motivation whatsoever to extend the range of solvents to tetrahydrofuran. *See, e.g.,* Solomon, col. 5 at lines 55-59 ("Suitable solvents to serve as the steeping medium for chlorhexidine base are water, methylene chloride and preferably methanol. For chlorhexidine salts ... suitable solvents are methanol, ethanol or preferably water."). Quite to the contrary, one of ordinary skill in the art would appreciate that many solvent solutions - including toxic and unstable solutions - which on its face meet the Examiner's criteria, simply would not be suitable for use in the present invention. Therefore, I disagree with the Examiner's conclusion that anyone would have considered as obvious the arbitrary selection of tetrahydrofuran and its combination with the formulations described in Solomon. I believe that persons of ordinary skill in the art would not, even having Solomon and the Merck Index at their disposal, have been guided to use tetrahydrofuran as a solvent in the present invention.

13. In sum, I believe that neither Solomon's disclosure nor the Merck Index - even in combination as proposed by the Examiner - would have suggested to a person of ordinary skill in the art (for example, a medical doctor) how to successfully achieve prolonged antimicrobial activity of a catheter by treating its surfaces with chlorhexidine, in particular treating the surface with the free base and water-soluble salt forms of chlorhexidine in a weight/weight ratio of between about 1:1 to about 1:5 as required by the presently claimed invention.

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14. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of any patent issuing from the above-captioned patent application.

8 / 10 / 04

Date

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